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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,586	12/20/2001	Vanessa Chisholm	P1746R1	1705

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EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 09/12/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/019,586	CHISHOLM ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *106-164* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *106-112,115-125, 128-129, 135-152 and 161-164* is/are rejected.

7)☒ Claim(s) *113,114,126,127,130-134 and 153-160* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *07/19/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Receipt is acknowledged of a response, filed 07/19/2005, canceling claims 1-105 and adding new claims 106-164. Thus, claims 106-164 are pending and under consideration in this action.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/19/2005 has been entered.

Information Disclosure Statement (IDS)

Receipt is acknowledged of an IDS, filed 07/19/2005. Applicant requests that the foreign language reference EP 0711835A and an English Language Abstract describing the reference be reviewed and a corresponding PTO Form 1449 be returned with the next action. The IDS lists the abstract corresponding for EP 0711835A, which abstract is reviewed and the listing for which is initialed in the corresponding Form PTO 1449. However, it must be noted that the EP 0711835A document has not otherwise been reviewed. Thus, the initialed PTO 1449 should only be construed to reflect that the abstract describing EP 0711835A has been reviewed.

Claim Objections

Claim 107, 160 and 163 are objected to because of the following informalities:

In claim 107, for the sake of consistency regarding the claims, the acronym "DHFR" should be amended to provide the corresponding definition, since it is in claim 107 that the limitation is first recited. Generally, it is only necessary to provide corresponding definitions for acronyms where they are firs recited in the claim set.

Claim 160 would be clearer if the term "where" were inserted before the phrase "the amount of RNA", and the verb "is" should also be inserted after "RNA" in the preceding phrase.

Claim 163 appears to missing the verb "is" before the term "indicative" in part *b*. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. **Claims 106-111 and 143-150 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Independent claim 106 is directed to a vector comprising a polynucleotide encoding a fusion polynucleotide consisting of a polynucleotide encoding GFP with a polynucleotide encoding an amplifiable selectable marker. The claims are vague and indefinite because the claim further recites that the polynucleotide encoding the desired product and the promoter are operably linked to the polynucleotide encoding an

amplifiable selectable marker *or* the polynucleotide encoding GFP. If the GFP and amplifiable selectable marker form a fusion polynucleotide, then it is unclear how the desired protein-promoter can be linked in the alternative to said GFP and amplifiable selectable marker (i.e., use of the conjunctive "or" in the claim). Put another way, if the GFP and amplifiable selectable marker comprise a fusion molecule, then a molecule (i.e., desired product-promoter) linked to GFP would also necessarily be linked to the amplifiable selectable marker.

The specification teaches that a fusion polynucleotide, for example with respect to GFP and the polynucleotide encoding DHFR, encodes a fusion protein of the GFP and amplifiable selectable proteins. (e.g., p. 24, l. 35; Figures 1-2). Indeed, without the clarification provided in the specification, one of skill could interpret a fusion polynucleotide to mean any stretch of DNA with/without intervening sequences that comprises a gene encoding a selectable amplifiable gene and gene encoding GFP.

In sum, the conjunction "or" confers ambiguity as explained above thus making indeterminable the claims' metes and bounds. Therefore as written, the claims are vague and indefinite.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

2. **Claims 112, 143-146, 151 and 161-164 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Tan et al. (US 6,235,967; hereinafter the '967 patent; reference of record).**

The limitation "operably linked" is interpreted as broadly as reasonable in view of the full disclosure. The limitation is not particularly delimiting with respect to the correlation of various structural elements on the claimed vector molecules. This interpretation is of record but it bears repeating herein. The term "operably linked" is explicitly defined in the specification, but the specification is as broad as the term itself. (Specification, p. 18, top). The specification provides the following definition:

> "Operably linked" refers to a juxtaposition of two or more components, ***wherein the components so described are in a relationship permitting them to function in their intended manner***. For example, a promoter and/or enhancer is operably linked to a coding sequence if it acts in cis to control or modulate the transcription of the linked sequence. ***Generally, but not necessarily***, the DNA sequences that are "operably linked" are contiguous and, where necessary to join two protein coding regions or in the case of a secretory leader, contiguous in reading frame. However, although an operably linked promoter is generally located upstream of the coding sequence, it is not necessarily contiguous with it. (emphasis added) (Specification, p. 18, ll. 1-8).

As the specification teaches, the components or elements comprising the vector do not have to be related in a contiguous manner. Furthermore, the requirement that the components are in a relationship permitting the components to function in their intended manner is quite broad. The definition provided is controlling insofar as any reasonable interpretation can be made with respect to the limitation "operably linked", for example, as long as the structural elements in a prior art vector *function in their intended manner.* Where several components are on the same plasmid or vector, and each component is "in a relationship permitting them to function in their intended manner" which literally

encompasses any combination/positioning of the components on the vector, as long as the components function in their intended manner. Therefore, the broadest reasonable interpretation would encompass a vector where components occur in any order. Thus, a promoter present on a vector would at least be operably linked to any other gene on the same vector, at least insofar as the structural elements are linked by virtue of being on the same vector molecule and at least insofar as each structural element functions in the intended manner (e.g., encoding a particular gene). For example, a clear case of where even the foregoing broad interpretation would not be met is where a gene encoding a protein is integrated into the chromosome comprising an inducible promoter and a dicistronic vector comprising GFP and DHFR such as in gene trap or promoter trap experiments. (See generally, Roos et al. Methods Enzym. 1997; 13:112-22, especially p. 114, Figure 1). As such, a vector comprising the claimed structural elements that function in their intended manner would read on the claimed invention. In sum, one cannot define the limitation "operably linked" as delimited to a promoter exclusively driving expression of a given gene, because the term is not defined in such an exclusive fashion.

With respect to limitations directed to splicing efficiency, it must be noted that where a prior art product teaches the limitation of an intron defined by 5' and 3' splice sites, splicing efficiency is a property that is considered intrinsic to said intron, the range of splicing for which is not something that the Office can determine.

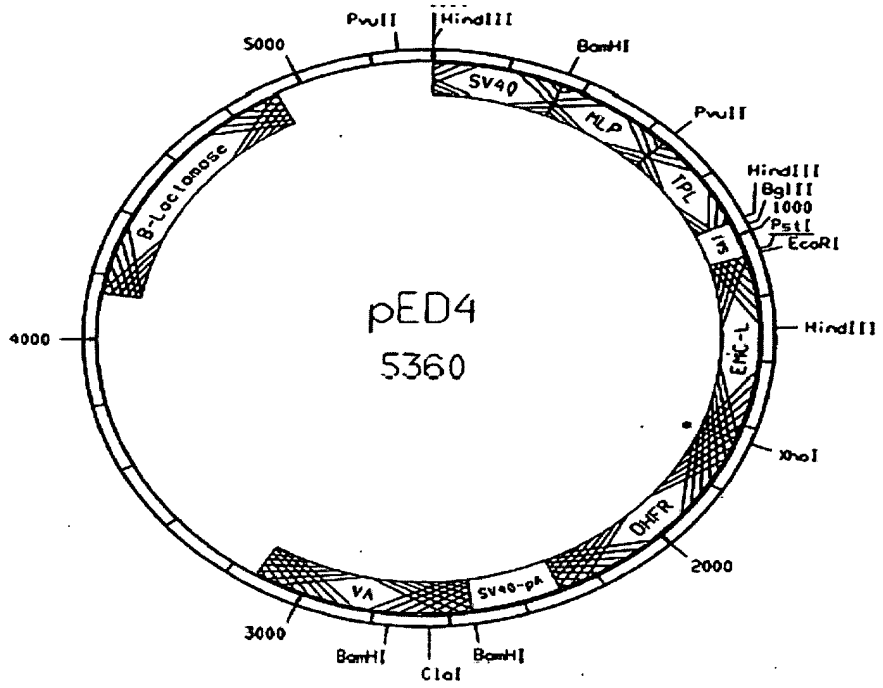
Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of

the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). In this case the difference at issue would be an intron in the prior art and the claimed intron with respect to splicing efficiency.

The '967 patent teaches a polynucleotide where GFP is fused to a selected sequence (e.g. methioninase or T antigen) and operably linked to a promoter. (e.g. Abstract; Fig. 1a). Furthermore, GFP can be of a higher fluorescence mutated (i.e. S65T) variety. (e.g. col. 3, l. 26). In addition, various cell types can be transfected with the polynucleotide, including methotrexate selected CHO cells. (e.g. col. 3, line 63; col. 6, ll. 27-37).

Furthermore, the '967 patent teaches using a DHFR-GFP dicistronic vector (e.g. col. 6, Example 1; showing GFP-S65T mobilization into pED-mtx^r) and explicitly teaches that such vector systems can be used to express proteins in mammalian cells. (e.g. col. 9, ll. 40-45). Thus one would have to examine the structure of the pED-mtx^r vector to understand the intrinsic structural properties of the dicistronic vector that the '967 patent teaches. The salient structural features of the vector that must be noted are the SV40 promoter marked by the HindIII restriction site, the adenovirus major later promoter (MLP), an intron composed of the 5' and 3' splice site (IVS), an internal ribosome entry site allowing for translation of inefficiently translated sequences (EMC-L), an amplifiable selectable marker (DHFR) and a polynucleotide encoding a desired product (VA an RNA gene). (Kaufman et al. Nuc. Acids Res. 1991; 19:4485-90, p. 4487, Figure 1 legend; reference of record).

As such the GFP-recipient vector teaches the claimed structural elements as depicted in the schematic that follows:



(supra, Kaufman et al. 1991, p. 4487, Figure 1).

The '967 patent teaches that GFP or mutant high intensity GFP are mobilized into pED-mtx^{r} at the PstI restriction site, just 5' of the internal ribosome entry site (EMC-L). (supra, col. 6, Example 1). Thus, the resulting vector would have the structural elements discussed in the preceding paragraph *and* would also comprise a polynucleotide encoding GFP. As such all the claimed structural limitations for claim 112 are met and as stated above, the vector can be transfected into CHO cells for DHFR amplification (i.e., with methotrexate). (e.g. col. 3, line 63; col. 6, ll. 27-37).

In addition, the reference teaches that an enzyme (i.e., methioninase) can be fused to GFP, thus meeting the claimed limitations of claims 161 and 162 (e.g., Fig. 1a).

With respect to the method claims (151, 163-164) the salient limitation is that expression of GFP and the amplifiable selectable marker is indicative of the cell also expressing the desired product, where the desired product is virtually any product encoded by the vector, other than the amplifiable selectable marker and the GFP protein. In the context of the instant reference, the vector is demonstrated to inherently comprise an SV40 and an adenoviral promoter element, each of which are active in mammalian cells. Further, it is demonstrated that the vector is clearly present in the transfected cells (e.g., through methotrexate selection and GFP selection).

Thus, based on the inherent properties of the vector, it must reasonably be assumed that the desired product of the VA gene is also present. As such, the claimed limitation is met where DHFR and GFP expression are indicative of a desired product also being present. In sum, the '967 patent anticipates the rejected claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. **Claims 112, 138-139, 143-147, 151 and 161-164 rejected under 35 U.S.C. 103(a) as being unpatentable over Tan et al. (US 6,235,967) as applied to claims 112, 143-146, 151 and 161-164 above, and further in view of Tan et al. (US 2004/0191173; hereinafter "173 Application").**

The '967 patent is applied to the claims consonant with the interpretations stated above. Additional embodiments are directed to the promoter element being a CMV promoter (claim 138) and that the desired product is selected from various proteins of interest (claims 139 and 147).

The '967 patent does not explicitly teach that the promoter can be CMV, which is commonly utilized in mammalian expression vectors in the prior art or that the GFP-modified pED-mtx^r mammalian expression vector can be utilized to express additional foreign genes (claims 139 and 147). However, the modifications necessary to mobilize a CMV promoter or any other foreign gene into a mammalian expression vector entail nothing more than routine experimentation.

Indeed, mammalian expression vectors utilizing a constitutive CMV promoter are routinely utilized in the art, as the '173 Application teaches. (e.g., p. 2, ¶ 0017). Further, an expression vector is utilized to express foreign genes of interest in mammalian cells. Clearly, the inventive step of the instant invention is not utilization of a routinely used promoter element or selecting a broad list of proteins that can be mobilized into an expression vector.

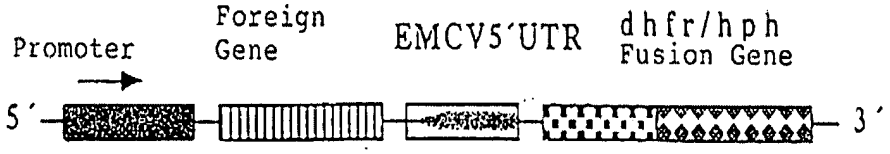
One of skill would have been motivated to modify the GFP-modified pED-mtx^r mammalian expression vector as taught by the '967 patent with a CMV promoter, a remedial step as suggested by the '173 Application, so as to obtain the benefit of an expanded range of constitutive promoters with known activity in mammalian cells. Further, one would have been motivated to express genes of interest in a mammalian expression vector whose primary purpose is to express genes of interest, so as to expand the range of proteins that can be expressed with a vector designed for gene expression.

Further, given the level of skill at the time of invention, one of skill would undertake nothing more than remedial steps to mobilize a CMV promoter element or genes encoding proteins of interest such as growth factors or enzymes. In sum, it would have been obvious to modify the dicistronic vector that the '967 patent teaches to incorporate a different routinely used promoter element and to incorporate various genes of interest.

4. **Claims 106-109, 111, 112, 138-139, 143-151 and 161-164 are rejected under 35 U.S.C. 103(a) as being unpatentable over Herlitschka et al. (US 6,114,146; see entire document; hereinafter the '146 patent) and further in view of Tan et al. (US 6,235,967, supra).**

The '146 patent teaches expression vectors, tansformed cells and methods of utilizing the same to produce foreign proteins in said transformed cells, wherein the expression vector contains a dicistronic transcription unit. (e.g., Abstract). More particularly, the '146 patent teaches a vector (i.e., polynucleotide) comprising a promoter, a foreign gene (i.e., selected sequence encoding a desired product) and a fusion gene comprising a first selectable gene and an amplifiable gene as is depicted in Figure 1:

FIG. 1



As the figure demonstrates, DHFR is fused with *hph* which is gene encoding an

antibiotic selectable protein, which functions as a non-amplifiable selectable marker. (col. 14, l. 65). The reference further teaches that an example of a foreign gene is human factor VIII, which meets the broad limitation of a receptor (e.g., Factor VIII binds a host of cellular factors, such as lipoprotein receptor-related protein). (e.g., col. 6, last ¶).

In addition, the reference teaches that the expression vector can comprise an IRES and an intron. (e.g., col. 5, ll. 6-30; col. 6, ll. 1-40). Further, the positioning of the IRES can be between the promoter element and the gene of interest. (Id.). With respect to splicing efficiency, it is deemed that a structural element having the same characteristics as the claimed structural element will function similarly, or that the intrinsic property of the splicing sites of the prior art intron meets the claimed limitation. Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977).

In addition, the '146 patent teaches that the expression vectors can be utilized to transform CHO cells (col. 5, ll. 1-8, ll. 15-31; col. 9, ll. 10-17), particularly DHFR deficient CHO cells (col. 5, l. 15). Further, the expression vectors can contain a CMV or SV40 promoter. (col. 6, ll. 3-6). With respect to the limitation for a "kit" neither claim 90 or the specification particularly define a kit. Therefore, the limitation is interpreted as broadly as reasonable to read on any container.

The '146 patent teaches the expression vectors are constructed utilizing restriction digests and ligation which reactions would necessarily be conducted in a reaction tube, thus meeting the limitation for a kit. (e.g., col. 10, Example 1, bridging to col. 11). The '146 patent explicitly states that the expression vectors have applicability in expressing foreign proteins in various cell culture systems. (e.g., col. 10, l. 34).

The reference does not explicitly teach that the fusion gene comprises GFP as the selectable marker versus an antibiotic resistance gene. Further, the reference does not explicitly recite that neuronotrophin-3, deoxyribonuclease, vascular endothelial factor, immunoglobulin or HER2 receptor can be expressed as desired proteins.

Regarding modifying the fusion gene of the '146 patent to include GFP as a selectable marker, GFP has been utilized routinely as a selectable marker in the prior art. As the '967 patent teaches, a dicistronic vector encoding GFP is utilized to identify (i.e., select) cells that are expressing the GFP protein. (e.g., e.g. col. 3, line 63; col. 6, l. 27).

As such it would have been obvious to replace one selectable marker (e.g., antibiotic resistance) with another selectable marker (fluorescent marker – GFP) to obtain the benefit of cell sorting via fluorescence. One of skill in the art would have been motivated to make such a modification so as to obtain the benefit of extending the range of potential selection markers utilized in a dicistronic vector expressing proteins in mammalian cells. Further, given the level of skill at the time of invention, there would have been a reasonable expectation of success in making such a modification, because the steps for making such a modification would have entailed nothing more than routine molecule biology (e.g., cutting and ligating an insert into the vector backbone).

Regarding expression of various proteins of interest, the salient point of the instantly claimed vector and the vector that the '146 patent teaches is defined by the structural elements discussed in the foregoing. In other words, the inventive step is not what particular foreign protein is being expressed, but primarily the vector, and the corresponding cells that are utilized to express a protein of interest (i.e., foreign gene). Furthermore, it would entail nothing more than routine and remedial steps to mobilize any given foreign gene (i.e., selected sequence) into the vector that the '146 patent teaches. Essentially, the vector that the '146 patent teaches is deemed to have the intrinsic characteristic insofar as it can be utilized to express any gene encoding a protein of interest.

As such, it would have been obvious to modify the vector that the '146 patent teaches to express, for example, a vascular endothelial growth factor (claims 81 and 89). One of skill would have been motivated to make such a modification in view of the '146 patent's suggestion that the vector has general applicability in expressing foreign genes in mammalian cells. Moreover, given the level of skill in the art at the time of invention, one of skill could simply mobilize any given gene into the vector that the '146 patent teaches. Thus there would be a reasonable expectation of success to conduct such a routine step entailing nothing more than cutting and ligating an insert to the vector backbone.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double

patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. **Claims 106-111, 115-125, 128-129, 135-143, 148-152, 161-164 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 59-71 and 80-92 of copending Application No. 10/714,000 in view of Tan et al. (US 6,235,967).**

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentably distinct from each other as discussed below.

With respect to instant claims 106-112, 143 and 148-151 and reference claims 59-71 and 80-92, independent instant claim 106 and reference claim 59 are respectively directed to a vector and polynucleotide comprising a fusion gene comprising a selectable gene and an amplifiable gene, a promoter and a selected sequence. Further, instant claim 106 merely delimits the selectable gene to be one of several known in the art, i.e., GFP. Dependent claims further delimit the amplifiable gene to be DHFR (e.g., instant claim 107: reference claim 60), define the intron site and its splicing efficiency (instant claims 108-109: reference claims 67-69) and further defining an internal ribosome entry (IRES) element (instant claim 111: reference claim 71). In addition, instant claim 112 more broadly recites that a selectable GFP gene and an amplifiable gene are contained on the vector but without the limitation of being comprised as a fusion gene (compare, reference claims 59, 66, 67, 69 and 71). Additional embodiments (instant claims 143, 148-151) are directed to cells and kits comprising the vector molecule or methods of producing a

selected sequence utilizing the vector molecule. Similarly, additional embodiments in the reference application (reference claims 80-92) are directed to cells, kits and methods of producing proteins of interest.

Instant independent claim 115 and independent reference claim 72 are respectively directed to vectors and polynculeotides comprising a first and second transcription unit, with a first and second intron, first and second promoter, a selected sequence of interest and a selectable gene and an amplifiable gene. The reference claim defines the selectable gene and amplifiable gene as comprising fusion genes, whereas the instant claim does not recite a fusion gene. However, instant claim 128 meets the limitation for a fusion gene comprising a selectable gene (GFP) and an amplifiable gene.

Additional embodiments are directed to the selectable gene as being mutated GFP or high fluorescence versions of the GFP (instant claims117, 119-121). The reference claims do no explicitly recite GFP or mutated version of GFP, but such selectable markers were routinely utilized in the prior art, as is taught by the '967 patent. (See, Rejection No. 2, supra). With respect to instant claim 128, the claim more particularly recites that the amplifiable and GFP are fused, thus the claims are all but delimited to the same structural elements, but for the more particular limitation of GFP.

In sum, the only difference between the claims is that the instant claims are directed to a vector versus a polynucleotide in the reference claims and that the instant claims are delimited to a particular selectable marker – GFP, which is well recognized as a selectable marker, as is taught by the '967 patent.

The '967 patent teaches that it would entail routine molecular biology steps to incorporate a GFP or modified GFP into a polynucleotide or vector molecule. (supra, Rejection No. 2).

Therefore, it would have been obvious to more particularly recite GFP as one of many prior art-recognized selectable markers in mammalian cell systems. Further, one would select variously available selectable markers such as GFP to extend the range and type of selectable marker (e.g., visual detection versus antibiotic resistance). Given, the level of skill in the art at the time of invention, it would entail nothing more than routine subcloning steps to mobilize one selectable gene versus another, thus there would have been a reasonable expectation of success in mobilizing GFP into a polynucleotide. Moreover, it would have been obvious to modify a polynucleotide into a vector so as to obtain the benefit of replication in cells, which also entails nothing more than remedial steps of subcloning a polynucleotide into a vector backbone as taught by the '967 patent.

6. **Claims 106-111, 138-143, 148-151 and 161-164 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 36-37, 39-41 and 47-52 of copending Application No. 10/715,270.**

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentably distinct from each other as discussed below.

Claims 106-111, 143, 148-151 and reference claims 40 and 47-56 are respectively directed to vectors, cells and methods of making proteins of interest and

methods of producing a host cell capable of producing a product of interest. The instant claims 106-111 are directed to vectors that are necessary to practice the methods of reference claims 36-37 and 39-41 and 47-52. Therefore, that the reference claims are directed to methods of producing a cell for production of a protein utilizing the same vectors does little to distinguish the instant and reference claims, whereby the end result in both sets of claims is that a protein of interest is produced utilizing the same vector and the same cells.

Reference claims 36-37 and 39 are directed to host cells or cell culture comprising the same, wherein the cells comprise a vector with the same structural elements of instant claims 106-111 (i.e., fusion gene comprising a selectable marker and an amplifiable gene, a promoter, encoding a produce of interest). Indeed, the primary difference between the instant and reference claims is that the reference claims rephrase a promoter to be transcriptional regulatory region and include a limitation directed to a termination site, but are otherwise indistinguishable with respect to the DNA construct being utilized. A promoter is of course a transcriptional regulatory region, as is evidence by subsequent reference claims. For example, instant claims and reference claims are directed to the promoter being a CMV promoter (instant claim 138: reference claim 52). Further, any gene encoding a protein or expression vectors utilized in the art would inherently comprise a termination sequence or site.

Independent reference claim 40 is directed to a method of producing a cell for production of protein of interest wherein a fusion molecule comprising the selectable gene and the amplifiable gene is positioned within an intron (compare instant claim 110). Additional embodiments are directed to the amplifiable gene being DHFR (e.g., instant

claim 107: reference claim 48-49). Additional embodiments are directed an antibody being produced from the methods of producing a protein or producing a cell for production of a protein (instant claim 139: reference claim 50).

In sum, the instant and reference claims are directed to patentably indistinguishable subject matter, because while the reference claims utilize different claim terminology (i.e., produce a cell for production of protein or transcription regulator region), the instant can reference claims are directed to patentably indistinguishable subject matter. The instant and reference claims utilize the same cells and the same vectors, with the singular objective of producing a selected protein of interest.

Allowable Subject Matter

Claims 113-114, 126-127, 130-134 and 153-160are objected to as being dependent from rejected claims, but would be allowable if rewritten in an independent form with all the intervening claim limitations. Claims 113-114 are directed to positioning an amplifiable gene or GFP respectively into the intron and further positioning respectively the GFP or amplifiable selectable gene 3' of the IRES element. Claims 126-127 similarly delimit positioning of GFP and the amplifiable gene. Claims 130-134 further delimit positioning of the IRES element and the gene encoding the desired product with respect to the first and second transcription units. Claims 153-160 are directed to isolating cells expressing GFP via an expression vector comprising a first and second transcription unit whereby steps for isolating the cells comprise the step of sorting and cloning the brightest 1-10% of fluorescent cells.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

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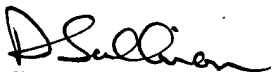
Respectfully submitted,
Ray Akhavan/AU 1636



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